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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,376	07/20/2001	Chi-Huey Wong	TSRI 663.1	4021

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,376	WONG ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 7-11 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 3-3-06, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-9, 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of synthesizing a polysialic acid product having alternating α2,9 and α 2,9 linkages of sialic acid using the "released" α2,9-2,9 polysialyltransferase (PST) isolated from *E.coli* K92, does not reasonably provide enablement for such a method in which a polysialyltransferase isolated from any or all sources including mutants, variants and recombinants, is used. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 7-9, 11 are so broad as to encompass the method of synthesizing a polysialic acid products with alternating 2,8-2,9 polysialic acids in which a PST isolated from any or all sources including mutants, variants and recombinants, is used. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of PSTs broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a single method of making a polysialic acid polymer using the specific enzyme isolated from *E.coli* K92. It would require undue experimentation of the skilled artisan to make (i.e., isolate the enzyme from any or all sources or make variants, mutants or recombinants of the *E.coli* K92 enzyme) and use such enzyme for making the sialic acid polymers. The specification is limited to teaching the use of *E.coli* K92 PST but provides no guidance with regard to the making of variants and mutants of the same. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the

claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass the use of the variants, mutants and recombinants of *E.coli* K92 PST because the specification does not establish: (A) regions of the *E.coli* K92 PST protein structure which may be modified without affecting PST activity; (B) the general tolerance of α2,8-2,9 PSTs to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including PSTs with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re*

Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of PSTs having the desired biological characteristics for use in the claimed method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection arguing that the kernel of the present invention is the "released" aspect of the α2,8/2,9 polysialyl-transferase and that the present application discloses for the first time that "released" α2,8/2,9 polysialyltransferase can be employed for synthesizing a polysialic acid product having alternating α2,9- and α2,8 linkages of sialic acid and that the use of such "released" α2,8/2,9 polysialyltransferase makes the claimed process much more efficient as compared to a process that employed membrane bound a2,8/2,9 polysialyltransferase, as employed in the prior art. Applicants argue that the examiner admits that claim 10 is enabled with respect to the use of "released" a2,8/2,9 polysialyltransferase from *Escherichia coli* K92 and that variants, mutations, and recombinants of a2,8/2,9 polysialyltransferase from *Escherichia coli* K92 are not required in order to practice the invention and that an applicant can not be expected to disclose and enable every non-essential variation of the claimed process. Examiner respectfully disagrees with such an argument. As applicants have observed, Examiner has indeed maintained that claim 10 is enabled because it is drawn to the use of "released" a2,8/2,9 polysialyltransferase from *Escherichia coli* K92 which applicants have disclosed and provide support for in the specification. However, the remaining claims, when given a broad interpretation (as the Examiner is expected to do) are not enabled because contrary to applicant's argument, these

claims read on variants, mutants and recombinants of any or all polysialyltransferase. Therefore, Examiner maintains that these claims are not enabled.

Claims 7-9, 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 7-9, 11 are directed to a method of making polysialic acid using a genus of PSTs which includes variants, mutants and recombinants of *E.coli* K92 PST. Claims 7-9, 11 are rejected under this section of 35 USC 112 because the claims are directed to a method in which a genus of polypeptides derived from *E.coli* K92 PST including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in *E.coli* K92 PST, that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of *E.coli* K92 PST has been provided by applicants which would indicate that they had possession of the genus of modified polypeptides for use in the claimed method. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from *E.coli* K92 PST, including fragments and variants within the scope of the genus for use in the claimed method. The genus of polypeptides for use in the claimed method is a large variable genus including peptides which can have a wide variety of structure. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species for use in the claimed method which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicants have traversed the above rejection arguing that the written description requirement for "released a2,8/2,9 polysialyltransferase" is supported in the specification at page 4, lines 10-19 and at page 4, lines 21-30. Examiner respectfully disagrees. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genera of 7-9, 11 includes species which are widely variant in structure. The genus claims 7-9, 11 is

structurally diverse as it encompasses polypeptides with polysialyltransferase activity from any or all sources and includes variants, mutants and recombinants having different structure. As such, neither the description of the function alone nor the disclosure solely of functional features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Hence the above rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-11 are rejected under 35 U.S.C. 103(a) as being obvious over Vann WF (FEMS Microbiology Lett., 1995, Vol. 128(2):163-166) or Steenbergen et al. (J.Bacteriol., 1992, Vol. 174(4):1099-1108) Van Dijk et al. (Analytical Biochem., 1981, Vol. 117(2):346-353) and the common knowledge in the art regarding the liberation or solubilization of insoluble membrane bound enzyme using detergents such as the non-ionic Triton-X. This rejection is based on the public availability of a printed documents. Claims 7-11 of the instant application are drawn to a method of making polysialic acid product linked through α 2,8/2,9 linkage by contacting a sialic acid acceptor and a CMP-sialic acid donor with a "released" (i.e., released from the membrane as a soluble form in the aqueous phase) α 2,8/2,9-polysialyltransferase isolated from any source, specifically using the one isolated from *E.coli* K92 for sequentially sialylating the sialic acid acceptor with CMP sialic acid donor followed by the step of removing the released CMP by treatment with alkaline phosphatase. It is well recognized in the art that the above strain of *E.coli* produces a unique polysialyltransferase which links sialic acid monomers through an

alternate α 2,8/2,9 linkage. The above two references of Vann and Steenbergen et al. teach the purification and characterization of the polysialyltransferase from *E.coli* K92 and describes the method of making polysialic acid product by contacting a sialic acid acceptor and a CMP-sialic acid donor with α 2,8/2,9-polysialyltransferase isolated from *E.coli* K92 for sequentially sialylating the sialic acid acceptor with CMP sialic acid donor. However, both the above references use the membrane bound form of the enzyme and use paper filtration and chromatography methods to separate the product formed as opposed to the step of removing the released CMP by treatment with alkaline phosphatase as claimed in the instant claims.

The reference of Van Dijk et al. teaches the use of alkaline phosphatase enzyme for removal of nucleotide phosphate and specifically from CMP nucleotide in a CMP-sialic hydrolase assay. Thus it appears that the use of phosphatase enzyme to remove the nucleotide sugars was well known in the art.

Therefore, combining the teachings of the above references along with the common knowledge in the art regarding solubilization of insoluble membrane bound enzymes with non-ionic detergent such as Triton X, it would have been obvious to those skilled in the art, specifically those involved in improving the method of Steenbergen et al. to treat the enzyme with said detergent to render it soluble and perform the synthesis. It would also be obvious tot those skilled in the art interested in developing a one-pot method or to develop an alternate method to that of Van Dijk et al. to treat the reaction mixture with alkaline phosphatase to remove the CMP side product. One of ordinary skill in the art would be motivated to do so because by treating the enzyme prep with detergent, the enzyme is available more for the reaction as well as to treat the enzyme reaction mixture with alkaline phosphatase enzyme since there is no loss of product formed and the product can be collected, further purified and used for several practical applications. One of ordinary skill in the art would have a reasonable expectation of success since Vann and Steenbergen et al. already put in place a method of

making the polysialic acid product and Van Dijk et al. suggest the use of alkaline phosphatase to remove the nucleotide sugars side product formed.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

In response to the previous rejection of the above claims, applicants have argued that The specification teaches that enzymatically active "released" a2,8/2,9 polysialyltransferase may be obtained by the use of detergent in combination with a hexameric histidine tag fused at the N-terminal end of such a2,8/2,9 polysialyltransferase (Specification, page 4, lines 10-19.) and that there is no teaching in the present application that enzymatically active "released" a2,8/2,9 polysialyltransferase may be obtained using detergent alone, i.e., in the absence of modification with the hexameric histidine tag or its functional equivalent and that Applicant is unaware of any support that the Examiner's suggested combination would be operable (inoperable?) with respect to the practice of the claimed process. Examiner respectfully disagrees with such a line of argument to be persuasive to overcome the above obviousness rejection. This is because, while applicants argue that enzymatically active "released" a2,8/2,9

polysialyltransferase *may* be obtained by the use of detergent in combination with a hexameric histidine tag fused at the N-terminal end of such a2,8/2,9 polysialyltransferase, claims are not limited to any such limitation. Furthermore, applicants have provided no scientific evidence or an argument as to why enzyme released as per the Examiner's obvious method would not lead to an enzymatically active "released" a2,8/2,9 polysialyltransferase. As explained in the above rejection, it is well known in the art that membrane bound insoluble proteins can be solubilized by treating with mild detergents such that the solubilized enzyme continue to be active. With such knowledge already available in the art and combining such knowledge with the teachings of the above reference it would have been obvious to one or ordinary skill in the art to arrive at the above claimed invention. Therefore, contrary to applicant's argument, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

Conclusion

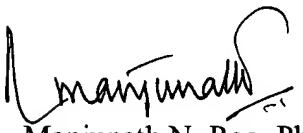
None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

May 10, 2006